DETAILED ACTION

Formal Matters

Applicants' response and amendments to the claims, filed 8/28/2009, are acknowledged and entered. Claims 10, 18-20, and 25 are pending and under examination.

Response to Arguments

Any previous rejections and/or objections to claims 11, 14-17, and 21-24 are withdrawn as being moot in light of Applicant's cancellation of the claims.

Applicants' arguments, filed 8/28/2009, have been fully considered but they are not deemed to be persuasive. Rejections and/or objections not reiterated from previous office actions are hereby withdrawn. The following rejections and/or objections are either reiterated or newly applied. They constitute the complete set presently being applied to the instant application.

Information Disclosure Statement

Receipt is acknowledged of the Information Disclosure Statement filed 8/28/2009. The Examiner has considered the references cited therein to the extent that each is a proper citation. Please see the attached USPTO Form 1449.

Claim Rejections - 35 USC § 103 - New Grounds of Rejection

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 10, 18-20, and 25 are rejected under 35 U.S.C. 103(a) as being unpatentable over **D'Amato** (USP No. 5,593,990; Issued 1/14/1997) (Reference A65 in IDS filed 10/24/2006) and **Kaplan *et al.*** (WO 92/14455; Published Sept. 3, 1992) in view of **Keane *et al.*** (Am. J. Respir.

Crit. Care Med., 2001, vol. 164, pages 2239-2242) and **Allen *et al.*** (Respir. Res., 2002, vol. 3, no. 13) (Reference C180 in IDS filed 12/23/2008).

The instant claims are drawn to treating idiopathic pulmonary fibrosis comprising orally administering to a patient having idiopathic pulmonary fibrosis 100-400 mg per day of thalidomide.

D'Amato discloses methods of inhibiting angiogenesis and treating disease states resulting from angiogenesis comprising administering thalidomide (Abstract; col. 4, lines 58-67; col. 5, lines 15-22). Administration of thalidomide and related compounds include standard routes of administration such as oral, topical, transdermal, or parenteral as recited in claim 19 (col. 12, lines 59-65). For oral administration to humans, D'Amato discloses doses of 0.1 to 300 mg/kg/day, most preferably 1 to 10 mg/kg/day (col. 13, lines 6-15). For an average human, the most preferable doses equate to approximately 70 to 700 mg/day, thus obviating the dose ranges recited in claims 10, 18, and 25. With respect to claim 20, D'Amato discloses formulations such as capsules, cachets, or tablets (col. 13, lines 30-36).

Kaplan *et al.* disclose methods for controlling abnormal concentrations of TNFα in human tissues comprising administration of compounds of Structure (II), which include thalidomide when R" is H and X is C=O (Abstract; page 7, lines 2-22; Figure 1-3). Similar to D'Amato, Kaplan *et al.* disclose the administration of compounds of the invention (*e.g.*, thalidomide) in carriers such as tablets, pills, and lozenges (page 21, lines 1-11).

The instant claims differ from D'Amato and Kaplan *et al.* in that neither reference expressly discloses the treatment of idiopathic pulmonary fibrosis.

However, Keane *et al.* teach that the pathology of idiopathic pulmonary fibrosis features dysregulated and abnormal repair with exaggerated angiogenesis, fibroproliferation, and deposition of extracellular matrix, leading to progressive fibrosis and loss of lung function (page 2239, left column). Evidence of neovascularization and extensive vascular remodeling has been observed in patient with interstitial fibrosis and during the pathogenesis of pulmonary fibrosis in a rat model of bleomycin-induced pulmonary fibrosis (*id.*). The authors disclose that administration of the angiostatic chemokine IP-10 leads to a reduction in pulmonary fibrosis that is mediated through inhibition of angiogenesis in a murine model of pulmonary fibrosis. (page 2239, right column). In the current study, the authors demonstrate that the angiogenic CXC

chemokine ENA-78 is elevated in idiopathic pulmonary fibrosis lung tissue and is associated with increased angiogenic activity (page 2241, left column).

Allen *et al.* teach that mice over-expressing TNF-α develop IPF-like fibrosis, whereas TNF-α-deficient or double TNF-α receptor knockout mice show resistance to bleomycin-induced fibrosis (page 3, right column of PDF submitted by Applicants). The authors further teach that promising results have been obtained by treating IPF patients with pirfenidone, a novel antifibrotic agent with anti-TNF-α properties (*id.*).

In light of the above cited prior art, it would have been *prima facie* obvious to one of ordinary skill in the art the time the invention was made to have used thalidomide to treat idiopathic pulmonary fibrosis. The skilled artisan would have been motivated to do so because thalidomide is suggested in the prior art to not only inhibit angiogenesis and thus is useful in the treatment of angiogenic-related disease and disorders (D'Amato) but to also inhibit TNF-α and thus is useful in the treatment of diseases and disorders characterized by abnormal TNF-α concentrations (Kaplan *et al.*). As both angiogenesis and TNF-α are implicated in the pathogenesis of idiopathic pulmonary fibrosis as evidenced by Keane *et al.* and Allen *et al.*, the skilled artisan would have been imbued with at least a reasonable expectation that a compound that inhibits both angiogenesis and TNF-α would be an effective treatment for idiopathic pulmonary fibrosis.

Response to Arguments

Applicant traverses the instant rejection, stating that the cited references fail to establish obviousness of each limitation found in the claimed subject matter: the oral administration of thalidomide in the recited dosages for the specific treatment of IPF. In support of this traversal, Applicant presents the following arguments.

Firstly, Applicant argues that neither D'Amato nor Kaplan teach or suggest the treatment of IPF. As correctly observed by Applicant, the Examiner acknowledged this fact. However, the instant rejection is based on a combination of references, not on the teachings of individual references taken alone. In response to applicant's arguments against the references individually, one cannot show nonobviousness by attacking references individually where the rejections are

based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.,* 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986). In the instant case, D'Amato and Kaplan are cited to show that the skilled artisan would know that thalidomide possesses antiangiogenic and anti-TNF-α activity. Keane and Allen are cited to show that both angiogenesis and overexpression of TNF-α are implicated in the pathogenesis of IPF. As such, it would have been *prima facie* obvious to one of ordinary skill in the art that a compound known to have antiangiogenic and anti-TNF-α activity would have efficacy in the treatment of IPF.

Secondly, Applicant alleges that D'Amato and Kaplan "teach away" from the claimed invention, because they are silent as to treating IPF, but only disclose numerous angiogenesis-related diseases or TNF-α-related diseases. In response, the Examiner respectfully submits that the skilled artisan would recognize the list of diseases disclosed in D'Amato and Kaplan are only *examples* of diseases contemplated to be treated by their inventions, not exhaustive lists. As evidenced by Keane and Allen, angiogenesis and overexpression of TNF-α are clearly implicated in the pathogenesis of IPF. As such, the skilled artisan would recognize IPF as a disease that could reasonably be treated by an inhibitor of angiogenesis and/or TNF-α production as disclosed in D'Amato and Kaplan.

Thirdly, Applicant argues that D'Amato does not provide a reason to specifically select thalidomide from the "plethora of the compounds" and general formula. Contrary to Applicant's allegations, D'Amato clearly and unequivocally provides such reasons to select thalidomide. In this regard, Applicant's attention is directed to Figure 1 of D'Amato, which explicitly discloses thalidomide as a compound useful in the invention (first compound on top row in Figure 1). Figures 6 and 7 demonstrate that thalidomide inhibits angiogenesis as described in D'Amato. D'Amato clearly and unequivocally considers thalidomide to be a "lead compound" wherein he states, "[O]ne embodiment of the present invention is the use of thalidomide or the metabolites of thalidomide to inhibit unwanted angiogenesis" (col. 6, lines 53-55). Accordingly, the Examiner is not persuaded by Applicant's argument that D'Amato does not provide a reason to select thalidomide from the compounds disclosed therein.

Fourthly, Applicant argues, similar to above, that Kaplan "merely discloses the use of broad genus of piperidine derivatives for controlling abnormal concentrations of TNF-α" and

thus "provides no reason to specifically select thalidomide from the laundry list of the compounds disclosed in the reference". Applicant's attention is directed to page 2, line 10 of Kaplan, wherein Kaplan teaches that 3-phthalimido-2,6-dioxo-piperidine (*i.e.*, thalidomide) is a preferred compound of the invention. Figures 1-3 of Kaplan demonstrate that thalidomide inhibits TNF-α production as described in Kaplan. Accordingly, the Examiner is not persuaded by Applicant's argument that Kaplan does not provide a reason to select thalidomide from the compounds disclosed therein.

Fifthly, Applicant argues that Keane and Allen do not cure the "defects" of D'Amato and Kaplan because they are silent about the use of thalidomide. Applicant is correct that the basis of the instant rejection is that it would have been obvious to administer thalidomide to patients having IPF, because Keane and Allen teach that angiogenesis (as taught in D'Amato) and TNF-α (as taught in Kaplan) are implicated in the pathogenesis of IPF, and angiostatic chemokine IP-10 and TNF-α inhibitor pirenidone showed promising results in treating IPF. Applicant questions why one skilled in the art would choose to pursue thalidomide over those agents. The Examiner is admittedly confused by this statement. If the Examiner were to take Applicant's reasoning, once a therapeutic agent is found to be effective for the treatment of a particular disease, those skilled in the art should not pursue other agents for the treatment of the same disease. However, this rationale is in direct contradiction to established medical science and research. Those skilled in the art are continuously pursuing new treatments for diseases, even if there already exists an effective treatment. The skilled artisan, recognizing that both angiogenesis and excessive TNF-α are implicated in IPF as taught in Keane and Allen, would have been motivated to administer a compound that effectively targets not one, but **two** different biological mechanisms of IPF pathogenesis. This is especially true when it was known that a compound that targets only one of these mechanisms (pirenidone) was effective in treating IPF.

Sixthly, Applicant alleges that the combined teachings do not provide the legally required reasonable expectation of success. This is not deemed to be persuasive because D'Amato and Kaplan demonstrate that thalidomide inhibits angiogenesis and TNF-α production in well-established models and teach, suggest, and motivate the treatment of angiogenesis-related diseases and disorders (D'Amato) and diseases and disorders resulting from excessive TNF-α

production (Kaplan). Keane and Allen clearly disclose that IPF is a disease that not only is angiogenesis-related, but also results from excessive TNF-α production. As such, the skilled artisan would reasonably expect a compound that targets both of these pathological mechanisms would be effective to treat IPF. This is especially true when it was known that a compound that targets only one of these mechanisms (pirenidone) was effective in treating IPF.

Seventhly, Applicant argues that the etiology of IPF and the mechanism of actions are unknown, and there are many cytokines associated with IPF. Applicant asserts that because D'Amato and Kaplan do not list IPF as a disease to be treated in their respective inventions, that a person of skill in the art would not recognize that angiogenesis or TNF-α is the primary factor responsible for IPF and/or that the use of an angiogenesis or TNF-α inhibitor would treat IPF. This is not deemed persuasive because, as noted above, Keane and Allen clearly teach that angiogenesis and TNF-α are implicated in the pathogenesis of IPF. Applicant has presented no factual evidence that such is not the case. In fact, the entire basis of Applicant's invention is the use of thalidomide to treat diseases and disorders "associated with undesired angiogenesis" and IPF is disclosed as one such disease, among many others. Furthermore, the prior art additionally teaches that an inhibitor of TNF-α, pirenidone, is effective in treating IPF.

Eighthly, Applicant argues that the rejections are not based on the proper teachings of the cited references but only with improper hindsight. In response to applicant's argument that the examiner's conclusion of obviousness is based upon improper hindsight reasoning, it must be recognized that any judgment on obviousness is in a sense necessarily a reconstruction based upon hindsight reasoning. But so long as it takes into account only knowledge which was within the level of ordinary skill at the time the claimed invention was made, and does not include knowledge gleaned only from the applicant's disclosure, such a reconstruction is proper. See *In re McLaughlin*, 443 F.2d 1392, 170 USPQ 209 (CCPA 1971). In the instant case, the Examiner has not relied on knowledge "gleaned only from the applicant's disclosure". The following teachings are explicit in the cited prior art and were known to those skilled in the art prior to Applicant's invention:

(i) Thalidomide is an inhibitor of angiogenesis suggested to be useful in treating diseases and disorders in which angiogenesis is implicated (D'Amato);

(ii) Thalidomide is an inhibitor of TNF-α production suggested to be useful in treating diseases and disorders in which excessive TNF-α production is implicated (Kaplan);

(iii) The pathology of idiopathic pulmonary fibrosis features dysregulated and abnormal repair with exaggerated angiogenesis, fibroproliferation, and deposition of extracellular matrix, leading to progressive fibrosis and loss of lung function (Keane); and

(iv) Mice over-expressing TNF-α develop IPF-like fibrosis, whereas TNF-α-deficient or double TNF-α receptor knockout mice show resistance to bleomycin-induced fibrosis and promising results have been obtained by treating IPF patients with pirfenidone, a novel antifibrotic agent with anti-TNF-α properties (Allen).

Applicant is respectfully requested to specifically point to where in the above analysis of the prior art the Examiner has relied on knowledge only gleaned from Applicant's disclosure, which is a requirement to establish *improper* hindsight reconstruction by the Examiner.

Ninthly, Applicant argues that the cited references do not teach or suggest other limitations of the claims. Specifically, Applicant alleges that the references fail to render obvious "key inventive limitations" found in the instant claims: orally administering thalidomide in the specific dosage range of 100 to 400 mg per day. These limitations are addressed in the above rejection: "For oral administration to humans, D'Amato discloses doses of 0.1 to 300 mg/kg/day, most preferably 1 to 10 mg/kg/day (col. 13, lines 6-15). For an average human, the most preferable doses equate to approximately 70 to 700 mg/day, thus obviating the dose ranges recited in claims 10, 18, and 25". Accordingly, the Examiner is not persuaded that "oral administration" of thalidomide in a dose range of "100 to 400 mg per day" is inventive over the cited prior art.

Applicant further argues that the instant claims recite, *inter alia*, the administration of a stereoisomer of thalidomide and that the Examiner has not established the obviousness of administering the recited stereoisomer. In response, the Examiner respectfully submits that no present claims under examination are limited to administration of a stereoisomer of thalidomide. Rather, independent claim 10 recites administration of thalidomide, or a pharmaceutically acceptable salt, or stereoisomer thereof. Accordingly, the claims are drawn to *optional* active

agents and the prior art need not teach all optional limitations because the Examiner has established a *prima facie* case of obviousness of at least one such recited option (*i.e.*, administration of thalidomide).

Lastly, Applicant argues that there are sufficient unexpected results to rebut even a *prima facie* case. In this regard, Applicant cites Horton *et al.* who reports a study where 11 patients with IPF were orally administered with thalidomide in 100-400 mg per day. The authors observed that 10 patients showed resolution of IPF with thalidomide. Applicant asserts that these results are sufficient to rebut any presumption of obviousness that may have been established by the references cited in the Office Action. In response, the Examiner respectfully questions what Applicant believes the result predicted by the cited prior art to be? The *prima facie* case set forth above clearly suggests and motivates the treatment of IPF with thalidomide, which would be predicted to be efficacious because it would target not one, but two different mechanisms involved in the pathogenesis of IPF. Horton *et al.* merely demonstrate that the treatment suggested and motivated by the cited prior art is effective. It is not apparent to the Examiner why Applicant believes this result to be "unexpected" in light of the teachings of the cited prior art.

Accordingly, the claims are deemed to be properly rejected as being unpatentable over D'Amato and Kaplan in view of Keane and Allen. The rejection is maintained for the reasons of record and as reiterated above.

Claims 10, 18-20, and 25 are rejected under 35 U.S.C. 103(a) as being unpatentable over **Banerjee *et al.*** (US 2004/0131614 A1; Published Jul. 8, 2004; Filed Jul. 18, 2003) in view of **Kaplan *et al.*** (WO 92/14455; Published Sept. 3, 1992) and **D'Amato** (USP No. 5,593,990; Issued 1/14/1997) (Reference A65 in IDS filed 10/24/2006).

Banerjee *et al.* disclose methods of treating pulmonary disorders comprising administering TNFα inhibitors, including TNFα antibodies (Abstract; page 2, [0014])). Such pulmonary disorders include idiopathic pulmonary fibrosis as recited in the instant claims (page 1, [0006]; page 2, [0014]-[0016]; page 12, [0102]-[0104]). With regard to combination therapy as recited in claim 11, Banerjee *et al.* disclose that the TNFα antibody is administered with at

least one additional therapeutic agent (page 2, [0018]). Doses of the disclosed anti-TNFα antibodies for administration to a patient having a pulmonary disorder range from 10-150 mg, more preferably 20-80 mg, and most preferably 40 mg, thus obviating the doses recited in claims 10, 18, and 25 (page 14, [0127]). With regard to additional therapeutic agents suitable for combination with the disclosed anti-TNFα antibodies, thalidomide as recited in the instant claims is one such therapeutic agent contemplated for combination with the treatment methods disclosed in Banerjee *et al.* (page 16, [0137]).

As further motivation to administer thalidomide in combination with an anti-TNFα antibody disclosed in Banerjee *et al.* for the treatment of idiopathic pulmonary fibrosis, the Examiner refers to Kaplan *et al.*, who disclose methods for controlling abnormal concentrations of TNFα in human tissues comprising administration of compounds of Structure (II), which include thalidomide when R" is H and X is C=O (Abstract; page 7, lines 2-22; Figure 1-3). Kaplan *et al.* disclose the administration of compounds of the invention (*e.g.*, thalidomide) in carriers such as tablets, pills, and lozenges (page 21, lines 1-11). With regard to claim 11, Kaplan *et al.* teach that a compound of the invention can be co-administered with another therapeutic agent effective to treat the condition associated with the debilitating effect (page 22, lines 9-23).

D'Amato discloses methods of inhibiting angiogenesis and treating disease states resulting from angiogenesis comprising administering thalidomide (Abstract; col. 4, lines 58-67; col. 5, lines 15-22). Administration of thalidomide and related compounds include standard routes of administration such as oral, topical, transdermal, or parenteral as recited in claim 19 (col. 12, lines 59-65). For oral administration to humans, D'Amato discloses doses of 0.1 to 300 mg/kg/day, most preferably 1 to 10 mg/kg/day (col. 13, lines 6-15). For an average human, the most preferable doses equate to approximately 70 to 700 mg/day, thus further obviating the dose ranges recited in claims 10, 18, and 25. With respect to claim 20, D'Amato discloses formulations such as capsules, cachets, or tablets (col. 13, lines 30-36).

Accordingly, it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to have administered a combination of an anti-TNFα antibody disclosed in Banerjee *et al.* and thalidomide as disclosed in both Banerjee *et al.* and Kaplan *et al.*

for the treatment of idiopathic pulmonary fibrosis. The skilled artisan would have been motivated to do so because Banerjee *et al.* teach that idiopathic pulmonary fibrosis is a disease associated with abnormal TNFα levels and thus provide a method for treating idiopathic pulmonary fibrosis comprising administration of an anti-TNFα antibody alone, or on combination with another therapeutic agent such as thalidomide. Kaplan *et al.* provide further motivation to select thalidomide for the combination therapy disclosed in Banerjee *et al.* wherein they disclose that thalidomide and related compounds are useful for treating diseases characterized by abnormal TNFα levels both alone and in combination with additional therapeutic agents.

In view of the above cited prior art, the skilled artisan would have been imbued with at least a reasonable expectation that a combination of an anti-TNFα antibody and thalidomide would be effective for the treatment of idiopathic pulmonary fibrosis.

Response to Arguments

Applicant traversed the previous rejection of claims 10, 11, and 19-24 as being unpatentable over Banerjee in view of Kaplan and claims 14-18 as being unpatentable over Banerjee in view of Kaplan as applied to claims 10, 11, and 19-24, further in view of D'Amato. This new ground of rejection of claims 10, 18-20, and 25 is necessitated by Applicant's amendment to claim 10, reciting the dose range of 100 to 400 mg per day and newly added claim 25. The Examiner will herein address Applicant's arguments as they pertain to the new ground of rejection.

Firstly, Applicant argues that amended claims 10 and 18-20 do not recite the use of a combination of a TNF-α antibody and thalidomide. This is not persuasive because independent claim 10 recites "comprises" language which allows for the administration of thalidomide in combination with another active agent, such as a TNF-a antibody as disclosed in Banerjee. Banerjee suggests that the TNF-α antibodies disclosed therein useful in the treatment of IPF can be combined with other therapeutic agent such as thalidomide as recited in the instant claims.

Secondly, with regard to the claimed dose range, as discussed *supra* D'Amato teaches that for oral administration to humans, doses of 0.1 to 300 mg/kg/day, most preferably 1 to 10

mg/kg/day (col. 13, lines 6-15). For an average human, the most preferable doses equate to approximately 70 to 700 mg/day, thus obviating the dose ranges recited in claims 10, 18, and 25. Accordingly, the Examiner is not persuaded that "oral administration" of thalidomide in a dose range of "100 to 400 mg per day" is inventive over the cited prior art.

Accordingly, the claims are deemed to be properly rejected as being unpatentable over Banerjee in view of Kaplan and D'Amato. The rejection is maintained for the reasons of record and as reiterated above.

Conclusion

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to JAMES D. ANDERSON whose telephone number is (571)272-9038. The examiner can normally be reached on MON-FRI 9:00 am - 5:00 pm EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ardin Marschel can be reached on 571-272-0718. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/James D Anderson/
Examiner, Art Unit 1614